# The Mizoroki-Heck reaction with internal olefins: Reactivities and stereoselectivities

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**Abstract:**
The Mizoroki-Heck(M-H) reaction is one of the most valuable reactions for functionalizin C-C double bonds in the presence of a Pd catalyst. This protocol is suitable for the reaction of a $C(sp^2)$-halide with a terminal olefin to produce a trans-1,2-disubstituted olefin. However, reports of the M-H reaction of internal olefins are rare and impractical due to low reactivity of internal olefin and problem of product diastereoselectivity. In this review, we summarise M-H reactions of internal olefins with aryl- or alkyl halides.
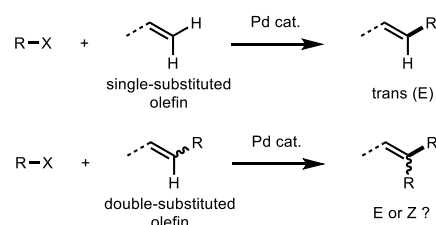
## 1. Introduction

The reaction of an organic halide and an olefin in the presence of palladium catalyst (or other transition metals) to produce a substituted alkene via oxidative addition, carbopalladation and β–H elimination is called the Mizoroki-Heck (M-H) reaction (Scheme 1) [1]. This incredibly useful reaction was discovered by Mizoroki[2] and Heck[3,4] independently. In 2010, Heck was awarded the Nobel prize in chemistry with Suzuki and Negishi[5]. Almost half a century has passed since the M-H reaction was discovered, but we can still see many reported new developments on the M-H reaction today.
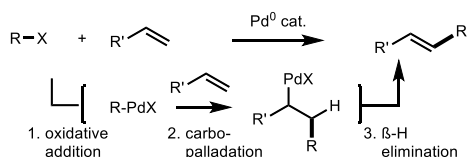


**Scheme 1.** The M-H reaction

Although considerable progress on the chemistry of the M-H reaction has been made, some issues remain unsolved. For example, terminal olefins (mono-substituted olefins) are excellent substrates for the M-H reaction giving trans alkene products, whereas internal olefins (1,2-disubstituted olefins) show low reactivity and the products are often produced as mixtures of stereoisomers (Scheme 2).

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**Scheme 2.** M-H reaction with terminal or internal olefins

In order to predict the stereochemistry in the M-H reaction of non-terminal olefins, a Newman projection is useful. When R-PdX adds to a *trans* internal olefin, the carbopalladation intermediate **A** is obtained. After C-C bond rotation of **A**, β–H elimination from **B** occurs to give the (*E*)-product. Similarly, the *Z*-product is obtained from a *cis* internal olefin via rotamer **D**. In most cases, the M-H reaction with internal olefins produces a mixture of (*E*) and (*Z*) products even from a single geometrical isomer of substrate. This is because the Pd catalyst can enable isomerization of *cis* internal olefins to *trans* internal olefins [6]. However, most M-H reactions of terminal dienes and 1-alkenyl halides in the presence of a Pd catalyst produce a single stereoisomer of the products, and do not suffer from stereoisomerization of the products [7]. In this short review, we will summarise a selection of examples of M-H reactions of aryl- and alkyl halides or arylboron reagents with internal olefins.
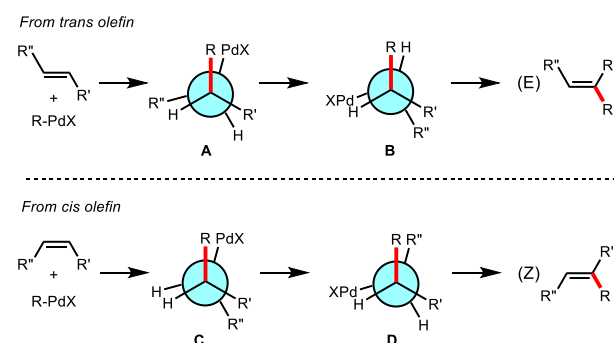


**Scheme 3.** Explanation of stereoselectivity in M-H reaction

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((Author Portrait))

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((Author Portrait))

## 2. M-H reaction with internal olefins

An internal olefin is less reactive compared to a terminal olefin due to steric hindrance. To circumvent this problem, various conditions have been developed. $P(t\text{-}Bu)_3$ is an electron-rich and highly bulky phosphine ligand, and effective for various cross-couplings[8]. In 2001, Fu reported a M-H reaction of internal olefins using a $Pd/P(t\text{-}Bu)_3$ catalyst system (Scheme 4)[9]. Ar-Br can be employed under the conditions even at room temperature. When (E)-internal olefins **4.1**, acrylates, are used, products are formed with highly E-selectivity **4.2** in good yields. The $Pd/P(t\text{-}Bu)_3$ catalyst system is also effective for the reaction of Ar-Cl at 120 ºC, in which (E)-**4.2** is predominantly generated.
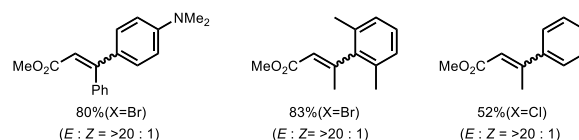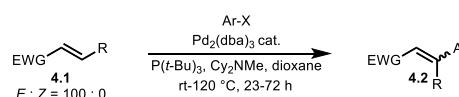
**Scheme 4.** $Pd/P(t\text{-}Bu)_3$ catalyst system

In aqueous media, a *p*-hydroxyacetophenone oxime-derived palladacycle catalyst is effective for the M-H reaction with internal olefins **5.1** (Scheme 5) [10]. β, β-diaryl products **5.2** are obtained in good yields under the conditions. Despite the use of (E)-substrates **5.1**, selectivities are not perfect. π-conjugated products **5.2** may undergo isomerization from (E) to (Z) at 120 ºC in the presence of the palladacycle.
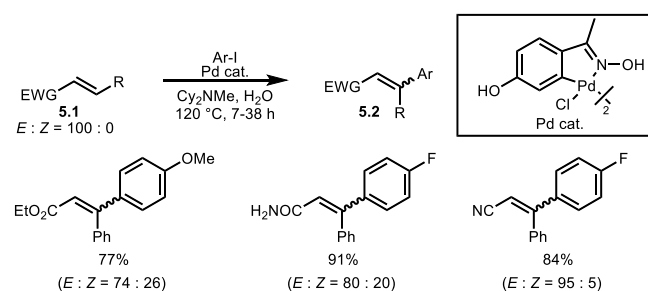
**Scheme 5.** *p*-Hydroxyacetophenone oxime-derived palladacycle catalyst system on water

An isoxazoline ligand with a ferrocene backbone enables Pd-catalyzed M-H reactions with internal olefins **6.1** (Scheme 6) [11]. β, β-diaryl products **6.2** are obtained in good yields and high selectivities. In this case, no (Z)-products **6.2** were detected, in contrast to the reaction shown in Scheme 5. The reason for the lack of isomerization is not explained in the paper, but the

catalyst bearing the isoxazoline ligand might not be an effective catalyst for isomerization of **6.2**.
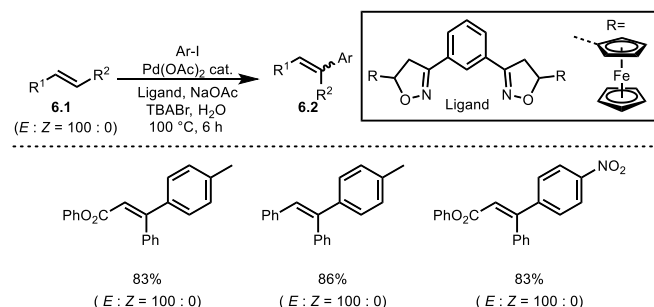
**Scheme 6.** Pd/isoxazoline ligand with ferrocene backbone catalyst system

Boronated aryl iodides can be coupled with internal olefins **7.1** to give boronated products **7.2** using a Pd/1,3-diketone ligand catalyst system (Scheme 7)[12]. Generally, $ArBF_3K$ is easily coupled with Ar-I, but boronated aryl iodides do not undergo Suzuki-Miyaura coupling in the presence of internal olefins **7.1**, from which M-H products **7.2** are obtained in good yields and with perfect (*E*)-selectivity. In this case, β, β-diaryl products **7.2** are not isomerized under the conditions.
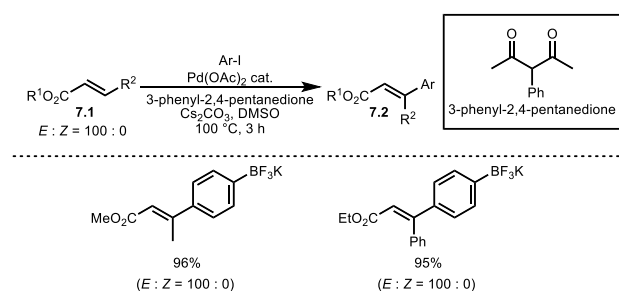
**Scheme 7.** The reaction with a diketone ligand

Fu's conditions (Scheme 4) enabled the M-H reaction of internal olefins and simple Ar-Br at room temperature in the presence of P(*t*-Bu)$_3$ as a ligand for a Pd catalyst. The reactions with internal olefins generally require higher reaction temperature over 100 °C due to the low reactivity of internal olefins. When the M-H reaction of internal olefin **8.1** and Ar-Br possessing a heterocycle or a phenol moiety was carried out in the presence of a Pd catalyst [Pd(tBu$_3$P)$_2$ or PdCl$_2$(DtBPF) (DtBPF=1,1'-bis(ditertbutylphosphino)ferrocene)] is carried out at 80 °C, products **8.2** are obtained in moderate yields due to catalyst poisoning but selectivities are perfect (Scheme 8) [13]. The M-H reaction of internal olefin **9.1** and electron-deficient Ar-Cl under Pd/DavePhos conditions also results in a moderate yield of **9.2** (Scheme 9) [14]. These results clearly illustrate the low reactivity of internal olefins for the M-H reaction. High reaction temperature (over 100 °C) or special ligands must be employed to achieve the M-H reaction of internal olefins with good yields.
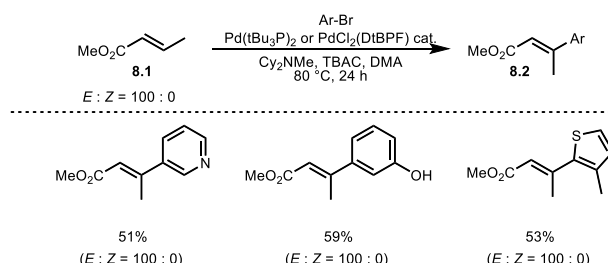
**Scheme 8.** The reaction with a heterocyclic substrate
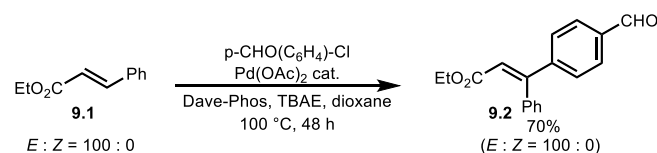
**Scheme 9.** The reaction in the presence of Buchwald's ligand

Simple Pd(OAc)$_2$ can be used in combination with AgOAc for M-H reactions with internal olefins **10.1** in AcOH at 110 °C (Scheme 10)[15]. Yields of products **10.2** are in a range between 92 to 98% but selectivities are moderate. Ligands, such as trialkylphosphine, are effective for increasing the catalyst reactivity in the M-H reaction with internal olefins, but the reaction of **10.1** and both electron-deficient and –rich Ar-I smoothly occurs without any ligands in this case. This highly reactive catalyst system can be explained by the generation of cationic Pd species from the reaction of Ar-Pd-I and a silver salt in AcOH. The reason for isomerization of the products is not clear but the activated cationic catalyst species might be responsible.
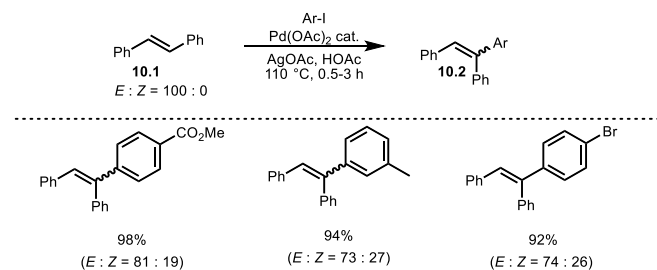
**Scheme 10.** The reaction in AcOH

Pd nano particles (NPs) are an attractive catalyst for transition metal-catalyzed cross-coupling reactions [16]. The reactivities

sometimes depend on the size of each particle but the catalytic activitiy does not exceed that of homogeneous catalysts in most cases. Nacci's group reported the M-H reaction of internal olefins **11.1** and ArCl in the presence of Pd NPs (Scheme 11) [17]. A tetrabutylammonium salt is a good stabilizer for small Pd NPs and good yields (80 to 94%) of **11.2** are obtained, but selectivities are not perfect probably due to the high activity of the catalyst. This reaction is a heterogeneous system but the catalyst cannot easily be recycled because of the particle size. Pd NPs can be embedded onto resin beads. These resin beads containing Pd NPs (SS-Pd) efficiently catalyze the M-H reaction with internal olefins **12.1** and the catalyst can be recycled after the reaction in this case (Scheme 12) [18]. The reactions smoothly occur with methyl substituted internal olefins **12.1** but selectivity is not perfect in the case of *p*-nitrophenyl substituted **12.1**.
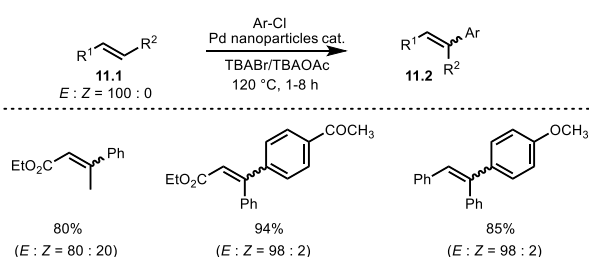


**Scheme 11.** Pd NPs as a catalyst
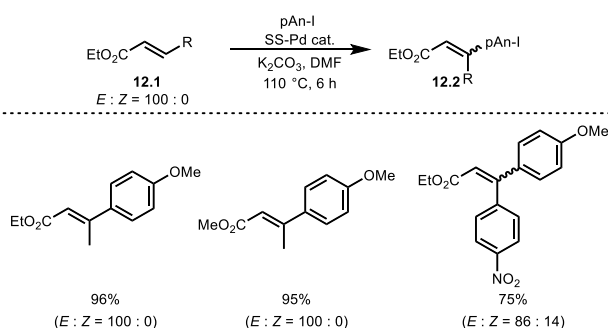


**Scheme 12.** SS-Pd as a catalyst

β-Aryl or alkyl substituted acrylamides (**13.1** and **14.1**) are also good substrates for the M-H reaction. Interestingly, reactivities and stereoselectivities of β-aryl or alkyl substituted acrylamides depend on the structure of the carboxamide moiety. For example, *N,N*-dimethyl β-aryl acrylamides **13.1** (R=Me) give the M-H product **13.2** with higher selectivity than the corresponding primary □□□□□ **13.2** (R=H) (Scheme 13) [19]. The authors explain that the different selectivities can be attributed to the coordination of the caboxamide group to Pd. This chelation effect is discussed below. On the other hand, the reaction of vinylic Weinreb amides **14.1** gives higher selectivities (Scheme

14) [20]. A Pd catalyst possessing an NHC ligand efficiently catalyzes the M-H reaction of **14.1** and ArI to produce the corresponding product **14.2** in good yield and with perfect selectivity. These perfect selectivities might be attributed to the chelation effect of the palladium catalyst to the Weinreb amide but the reason is not clear.
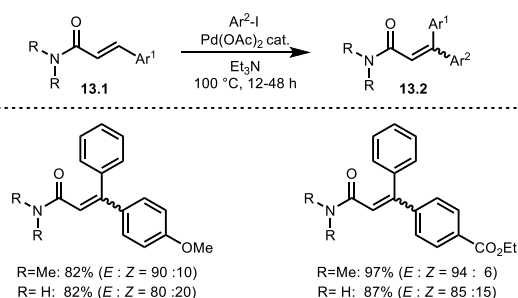


**Scheme 13.** The reaction with acrylamide
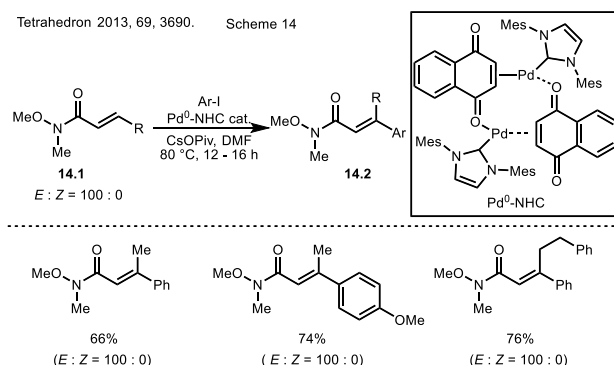


**Scheme 14.** The reaction with a NHC ligand

The reactivities of styrene, acrylonitrile, and acrylate possessing a vinylic ether moiety (**15.1**, **15.2** and **15.3**) were examined in the M-H reaction with a Pd/tetraphosphine (Tedicyp) catalyst system (Scheme 15) [21]. The reaction of **15.1** ($E{:}Z$ = 98:2) resulted in the product **15.4** in 58% yield ($E{:}Z$ = 35:65). Similarly, lower selectivities are observed in the reaction of **15.2** and **15.3**. The electronic properties of the ether functional group might affect the diastereoselectivities in these reactions.
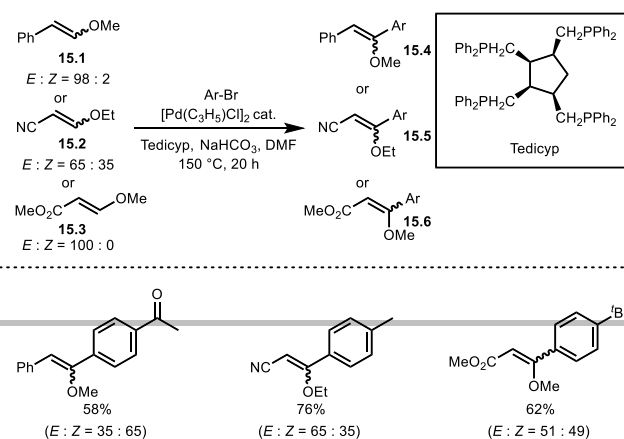
**Scheme 15.** The reaction with Tedicyp ligand

A Pd/carbethoxyurea (CEPU) catalyst system is effective for carrying out the M-H reaction with internal olefins. In this system, β-substituted-α,β-unsaturated aldehydes and esters (**16.1**) can be applied to the reaction (Scheme 16) [22]. The chemical yields of **16.2** are good but the selectivities are very low. Moreover, only electron-rich aryl iodides show reactivity for internal olefins. The conditions including solvent, base, and reaction temperature are slightly different from other reports of M-H reactions with internal olefins, but selectivities cannot be controlled under these conditions. The Pd/CEPU catalyst system may catalyze isomerization of the products **16.2**.
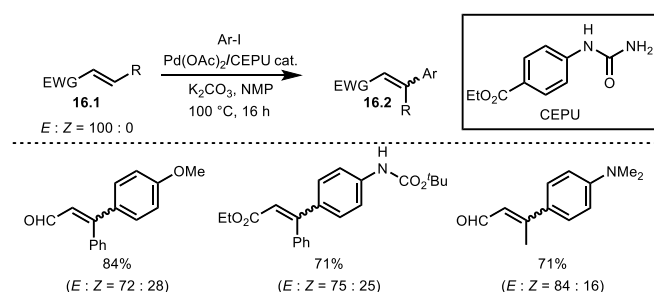


**Scheme 16.** The reaction with CEPU ligand

Unprotected functional groups including amines, alcohols, phenols, thiols, and carboxylic acids sometimes affect the catalyst activities for transition-metal catalyzed reactions. An ionic liquid as a reaction solvent enables M-H reaction with β-substituted-α,β-unsaturated carboxylic acids **17.1** as the internal olefin (Scheme 17) [23]. The reaction of **17.1** and aryl iodide in the presence of the Pd catalyst gives the corresponding coupling product **17.2** at 120 °C. The chemical yields of **17.2** are moderate but selectivities are good.
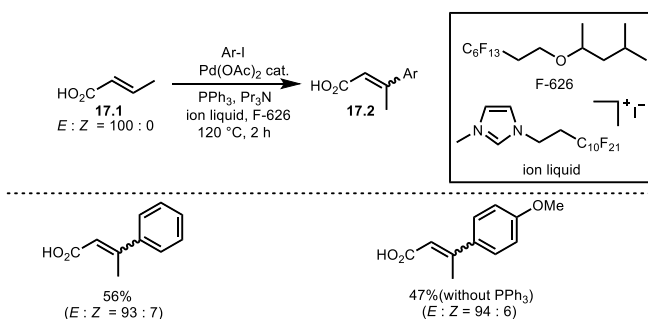


**Scheme 17.** The reaction in ionic liquid

Sulfur compounds, such as β-substituted-α,β-unsaturated sulfoxides also react with aryl halides in the presence of a Pd catalyst to give M-H products. For example, β-substituted-α,β-unsaturated sulfoxides **18.1** possessing *N,N*-dimethylaniline as a directing group react smoothly with ArI to produce the corresponding products **18.2** in moderate yields with good selectivities (Scheme 18) [24]. The amine directing group is necessary to increase the reactivity of the sulfoxide substrate in the presence of the Pd/dppf catalyst. The M-H reaction of α,β-substituted-α,β-unsaturated sulfoxides without a directing group requires Fu's conditions (Pd/P(t-Bu)$_3$). For example, the reactions of **19.1** and ArBr smoothly produce M-H products **19.2** in the presence of P(t-Bu)$_3$ but the reaction even with a terminal olefin does not occur with a Pd/PPh$_3$ catalyst system (Scheme 19) [25].
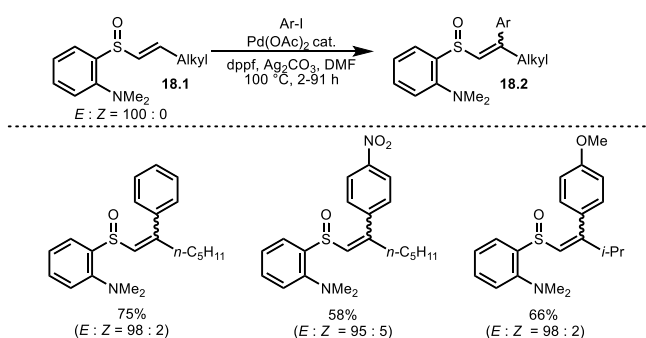


**Scheme 18.** The reactivity of sulfoxide substrate possessing dimethylamino group
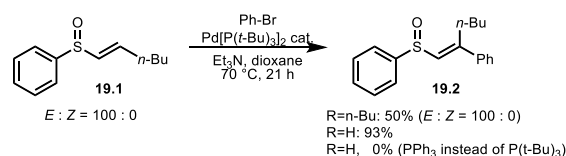


**Scheme 19.** The reactivity of sulfoxide substrate

Vinylic boron reagents are one of the most attractive reactants for the M-H reaction because the corresponding boronated products can be used for further transformations via Suzuki-Miyaura coupling. The reactions of vinylic MIDA boronates **20.1** with ArI under a Pd(OAc)$_2$/AgOAc catalyst system produces **20.2** in good yields with moderate to good selectivities (Scheme 20) [26]. The reaction is carried out at 80 °C without special ligands, such as trialkylphosphines, but the results are good.
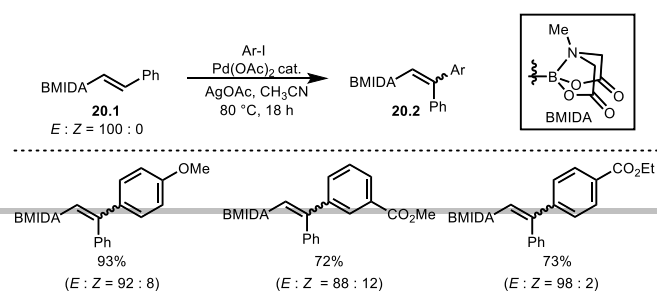
**Scheme 20.** The reaction with aryl-BMIDA

Various β-substituted-α,β-unsaturated compounds can be employed for the M-H reaction, and results are mostly good as outlined above. On the other hand, aryl electrophiles other than aryl halides can be also applicable to the reaction under Pd catalyst conditions. Arylsulfonyl hydrazides (ArSO$_2$NHNH$_2$) are good reagents for the M-H reaction in the presence of a Pd catalyst (Scheme 21) [27]. In this reaction, an active arylpalladium acetate is generated after the releasing of SO$_2$ and N$_2$ from *in situ* generated ArSO$_2$NHNH-Pd-OAc, which is generated from the reaction of ArSO$_2$NHNH$_2$ and Pd(OAc)$_2$ under oxygen atmosphere at 70 ºC. The resulting arylpalladium acetate reacts with **21.1** to produce **21.2** in moderate yields and with perfect selectivities. Aryldiazonium tetrafluoroborates are also very effective electrophiles for the M-H reaction (Scheme 22 and 23) [28,29]. In this reaction, a mono-cationic arylpalladium species is generated from the reaction of Pd$^0$ and an aryldiazonium tetrafluoroborate. This cationic palladium is more reactive towards an olefin compared than a neutral one [30]. Therefore, aryldiazonium tetrafluoroborates are considered to be the best aryl electrophile in the M-H reaction with unreactive internal olefins. For example, electron-rich aryldiazonium salts undergo M-H reaction of internal olefins (**22.1**) under reflux conditions in MeOH (Scheme 22). But electron-deficient ones react with **22.1** at room temperature without special ligands, such as P(*t*-Bu)$_3$. On the other hand, the M-H reaction of aryldiazonium tetrafluoroborates and **23.1** in the presence of NaOAc as a base and MeOH/MeCN as a solvent occurs at 70 ºC (Scheme 23). Both of the reactions shown in Scheme 22 and 23 produce the corresponding products (**22.2** and **22.3**) in good yields with selectivties ranging from moderate to good.
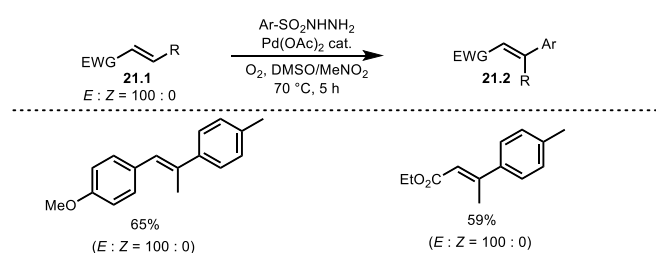
**Scheme 21.** The reaction with ArSO$_2$NHNH$_2$
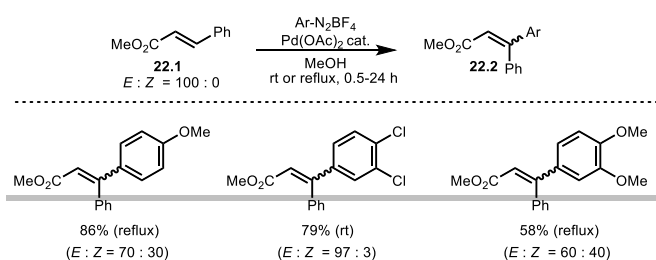
**Scheme 22.** The reaction with ArN$_2$BF$_4$
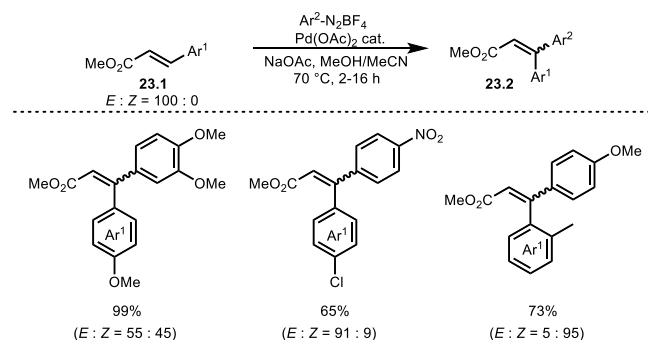
**Scheme 23.** The reaction with ArN$_2$BF$_4$ in the presence of NaOAc

## 3. Chelation-controlled M-H reaction

Tuning of reaction conditions can be very effective for carrying out M-H reactions with poorly reactive internal olefins. Another methodology to overcome poor reactivity of internal olefins is to use a directing group, which provides a chelation effect to increase the coordination ability of Ar-PdX towards a C-C double bond (Figure 1). After the coordination of Ar-PdX to the alkene, carbopalladation smoothly occurs at the β-position with respect to the directing group.
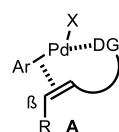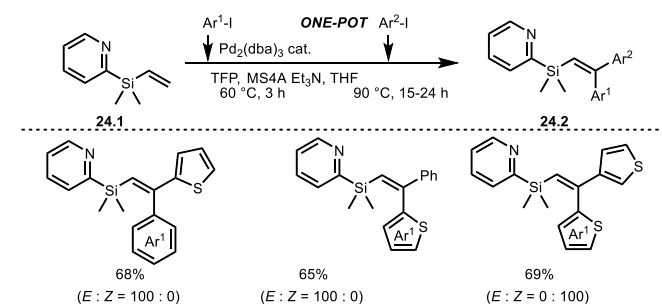
Enhancing reactivity of internal olefin
100% ß-selective

**Figure 1.** Effect of a directing group

Pyridine and pyrimidine are good directing groups for M-H reactions with internal olefins. Itami and Yoshida's group reported the one-pot reaction of pyridyl(vinyl)silanes or pyrimidyl(vinyl)sulfides and two different Ar-I to produce trisubstituted olefins in the presence of a Pd catalyst (Scheme 24 and 25)[31,32]. The first reaction of **24.1** with Ar$^1$-I produces the *trans* M-H product. The following arylation with Ar$^2$-I produces **24.2** in good yields with perfect *E*-selectivity (Scheme 24). Similarly, pyrimidyl(vinyl)sulfides react with two different aryl iodides (Shceme 25). The results of one-pot double M-H

reactions are perfectly stereo- and regioselective with the aid of the directing group. Both pyridylsilyl groups and pyrimidylsulfide groups can be utilized for further cross-couplings with Grignard reagents or aryl halides in the presence of a Pd catalyst.



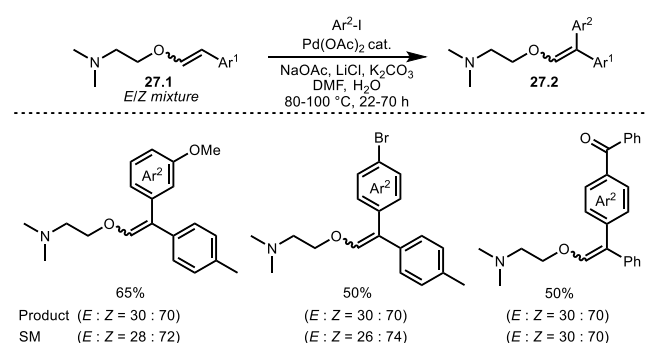**Scheme 24.** Substrate possessing pyridyl group
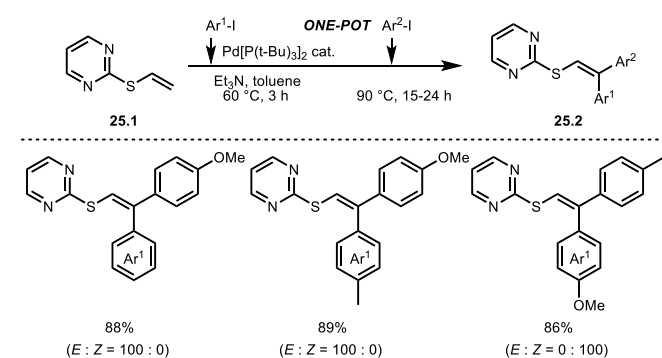


**Scheme 25.** Substrate possessing pyrimidyl group

The M-H reaction of internal olefins typically gives (*E*)-selectivity. To obtain the (*Z*)-product from the reaction of an internal olefin and an aryl halide, a vinylic C-H functionalization process is one of the most promising approaches. The reaction of *trans* 2-vinylic pyridine **26.1** and an aryl bromide in the presence of a Ru catalyst leads to a vinylic C-H arylation reaction to produce a (*Z*)-arylated product **26.2** in good yield and with perfect selectivity (Scheme 26)[33]. The reaction of (*E*)-stilbene and ArBr results in no product, which indicates the importance of the pyridyl group as a directing group. A key intermediate of this reaction is a nitrogen-atom coordinated ruthenacycle via ruthenation of the vinylic hydrogen of **26.1**. This C-H functionalization methodology gives complementary (*E*,*Z*)-selectivity to the M-H reaction.
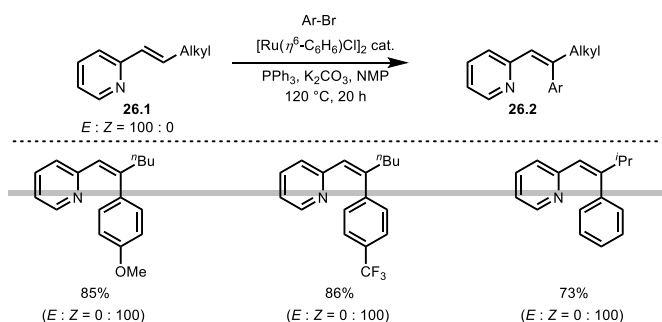


**Scheme 26.** 2-Pyridyl directing group for Ru-catalyzed reaction

In the M-H reactions, *E* substrates are employed to obtain a single diastereomer. When the reaction is carried out with *E*,*Z*-mixed substrates **27.1**, (*E*,*Z*)-mixed products are obtained, in which (*E*) and (*Z*) ratios of substrates are matched with those of the starting material **27.1** (Scheme 27)[34]. The reaction is not convergent, which indicates that the formation of a C-C double bond via β–H elimination is quite predictable.



**Scheme 27.** Substrate possessing dimethylaminoethyl group

As was shown in Scheme 18 and 19, the *N,N*-dimethylamino group was effective as a directing group in the reaction of β-substituted-α,β-unsaturated sulfoxides **18.1** and aryl halides. The M-H reaction of β-substituted-α,β-unsaturated sulfones **28.1** possessing a *N,N*-dimethylaniline group gives the corresponding (*E*)-products **28.2** in good yields with perfect selectivities (Scheme 28)[35]. An *N*-coordinated palladacycle is generated after arylpalladation to **28.1** to produce (*E*)-**28.2** exclusively. The presence of a silver salt is important to generate a cationic palladium species, which undergoes facile coordination to the olefin and amino directing group.
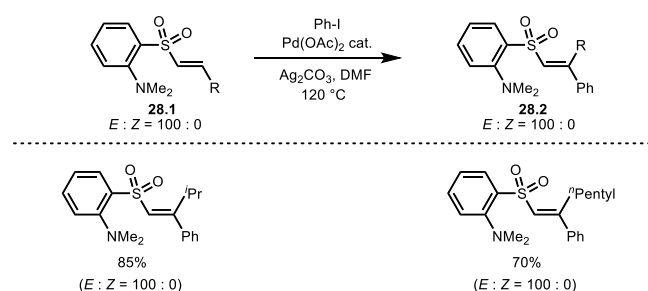


**Scheme 28.** Substrates possessing a dimethylaniline group

# 4. Heck reaction with arylboron or -silicon reagents

Aryl halides are good coupling partners for the M-H reaction, but arylboron or –silicon reagents are also applicable to the reaction in the presence of a appropriate oxidant. The reaction of an arylboron or –silicon reagent and $PdX_2$ produces Ar-PdX via a transmetallation process. After carbopalladation followed by β-H elimination, the corresponding Heck product and $Pd^0$ (after reductive elimination of HPdX) are generated. An oxidant is required to regenerate a $Pd^{II}$ species to start a $2^{nd}$ catalytic cycle. This type of the reaction is referred to as an oxidative Heck reaction. Heck originally employed the reaction involving a transmetallation process with arylmercury, -tin, and other species [36] and generally employed terminal olefins to obtain *trans* products in good yields. The reaction is also unsuitable for internal olefins like the original M-H reaction. Therefore, most of the reactions shown in this section require high temperatures to obtain good yields of the M-H products. To increase the reactivity of less reactive internal olefins, a directing group is effective, as was shown in section 3. For example, amidomethyl substituted acrylates **29.1** react smoothly with arylboronic acids at room temperature in the presence of a Pd catalyst and TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) as an oxidant (Scheme 29)[37]. In this reaction, only (*E*)-products are obtained from (*E*)-**29.1**. This mild reaction is attributed to the effect of the aminomethyl directing group.
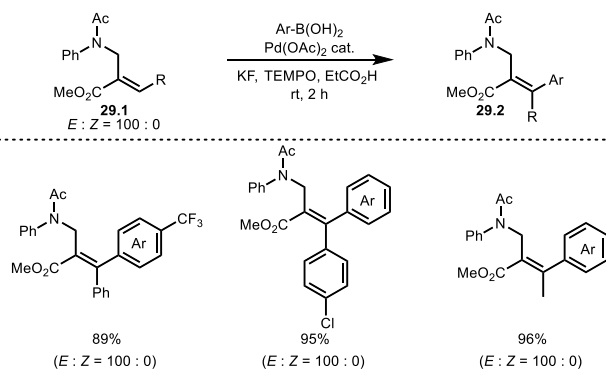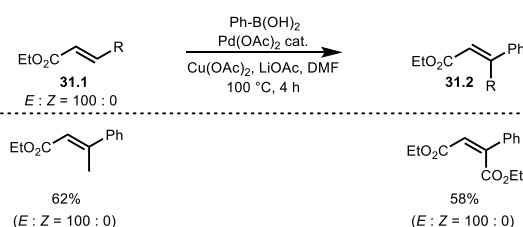
**Scheme 29.** The reaction in the presence of tempo as an oxidant

The nature of the arylboronic acid and olefin structure (having a directing group or not) influences the reactivity and the product selectivity. Tuning the reaction conditions also affects the reaction. Studer's group reported that 4-hydroxylated TEMPO as an oxidant and a carboxylic acid as a solvent are most effective to carry out the oxidative Heck reaction at room temperature (Scheme 30)[38]. This condition is very effective to obtain the product **30.2** from styrene derivatives **30.1** in good yields and selectivities, but the reason for this high reactivity is unclear.
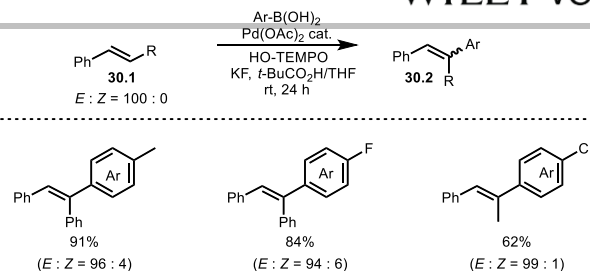
**Scheme 30.** The effect of modified tempo as an oxidant

Copper is employed as an oxidant for the reaction of acrylate derivatives **31.1** (Scheme 31)[39]. The reactions of **31.1** and arylboronic acids in the presence of a Pd catalyst and excess $Cu(OAc)_2$ give the corresponding Heck products **31.2** in moderate yields with perfect (*E*)-selectivities. In the case of substituted enamides **32.1**, $Cu(OAc)_2$ is also effective as a catalytic oxidant in combination with oxygen (Scheme 32)[40]. This enamide group in **32.1** could act as a directing group but increased reactivity of the substrate is not observed. The yields and selectivities of **32.1** are high under the conditions. In both cases, copper did not affect the diastereoselectivities.

**Scheme 31.** The reaction in the presence of Cu as an oxidant
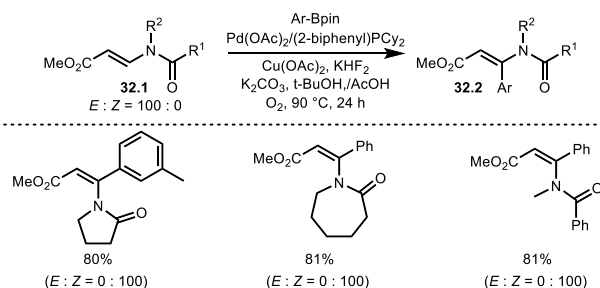
**Scheme 32.** The reaction with enamide

Strong acid as a solvent is effective for carrying out an oxidative Heck reaction without any oxidant. When arylboronic acids react with **33.1** in $CF_3CO_2H$ (TFA), the corresponding Heck products **33.2** are produced in a good yields with perfect (*E*)-selectivities (Scheme 33)[41]. To complete the catalytic cycle, an oxidant is required to re-generate a $Pd^{II}$ species, because the H-$Pd^{II}$-X species after β–H elimination readily converts into $Pd^0$ and HX. The resulting $Pd^0$ species needs to be oxidized by an oxidant to generate a $Pd^{II}$ species, but the reaction of TFA and H-$Pd^{II}$-X can potentially generate a X-$Pd^{II}$-X species directly [42], which can undergo transmetallation with the arylboronic acid .
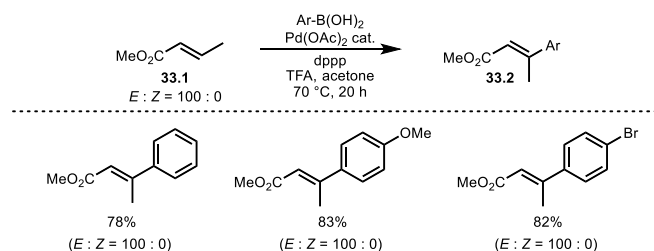
**Scheme 33.** The reaction in strong acid

Organosilicon reagents are also good aryl donors for the oxidative Heck reaction. The reaction of arylsilanols and **34.1** in the presence of a Pd catalyst and a copper oxidant gave Heck products **34.2** in moderate to good yields (Scheme 34)[43]. In the case of the reaction with fumarate, the product selectivity is perfect, but crotonate gives ($E$) and ($Z$)-mixtures of **34.2**. The oxidative Heck reactions with arylboron and –tin reagents sometimes suffer from homocoupling side reactions to give $Ar_2$. A key benefit of the arylsilicon reagents is that they do not form ahomocoupling product in the reaction.
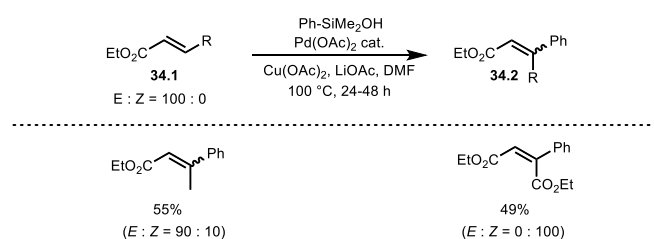


**Scheme 34.** Arylsilanol as an aryl donor

## 5. Alkylative M-H reaction

It is well known that alkylation is one of the most challenging reactions in transition metal-catalyzed chemistry. Alkylative M-H reactions [1a] [44] have been studied, but it is very difficult to obtain the corresponding products with good yields because of the strong tendency of the alkylmetal intermediate to undergo "β-hydride elimination reaction" during the reactions. Although many chemists have devoted their energy to this field, existing methodologies almost always employ a combination of terminal olefins and alkyl halides. Only a few examples of reactions with internal olefins have been described. Moreover, the reaction mechanism is sometimes different from the original M-H reaction, as it involves alkyl radical generation followed by the addition to the olefin then hydrogen elimination. The alkylative M-H reaction can therefore be distinguished from the original M-H reaction[1a], but the mechanistic details of alkylative M-H reactions will not be discussed in this review.

The reaction of a secondary alkyl iodide (cyclohexyl iodide) and β-methyl styrene (**35.1**) gives ($E$)-product **35.2** in 17% yield under irradiation conditions (Scheme 35) [45]. In this reaction, no Pd catalyst is needed, and a free radical mechanism is operative. When terminal olefins, such as styrene derivatives, are employed, good yields of the products are obtained. On the other hand, Pd catalyst conditions are used instead of irradiation

in the reaction of *trans* crotonates **36.1** with alkyl iodides. The corresponding products **36.2** are obtained in good yield, but the selectivities are low (Scheme 36) [46]. This reaction is also likely to proceed through a radical pathway. Unlike arylative M-H reactions, selectivities cannot readily be controlled in these processes.
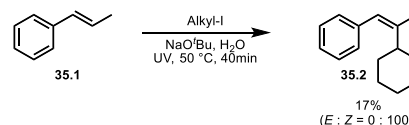


**Scheme 35.** Alkylation uder UV irradiation
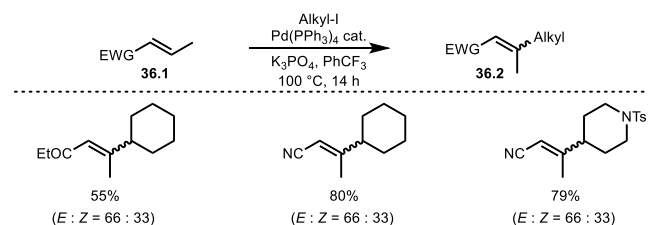


**Scheme 36.** Alkylation with e-deficient olefins

The reactivities of ($E$)- and ($Z$)-olefins are sometimes different from each other. For example, ($Z$)-enamide **37.1a** reacts with a bromomalonate ester possessing a secondary-alkyl moiety to produce 68% yield of **37.2a** but the reaction with ($E$)-enamide **37.1b** does not give any products (Scheme 37) [47]. Both of the reactions occur under photo irradiation conditions, and the key intermediate is a radical species generated from the bromomalonate ester. Curiously, the radical species does not appear to react with the ($E$)-olefin at all. In this reaction, bromomalonates possessing a tertiary-alkyl moiety can also react with ($E$)-**37.1** in good yield with perfect ($E$)-selectivities. On the other hand a tertiary alkyl group, 1-bromoadamantane, reacts with β-methylstyrene **38.1** to produce **38.2** in a moderate 15% yield with perfect ($E$)-selectivity (Scheme 38) [48]. Unlike the photoredox system in Scheme 37, a simple Pd catalyst system is generally not suitable for alkylation of a internal olefin.
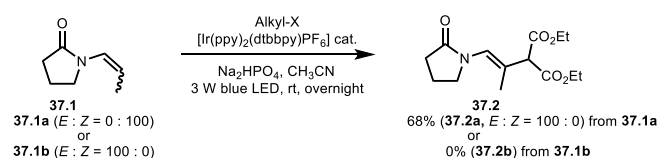


**Scheme 37.** Alkylation with enamide
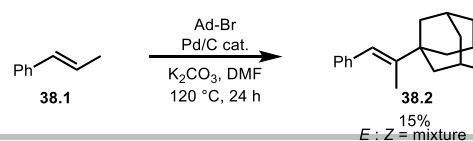
**Scheme 38.** Tertiary alkylation

To obtain stereoselective and high yielding alkylation reactions, a directed C-H alkylation is one of the few successful methodologies. This is out of main focus of this review, but the concept is illustrated by the example shown (Scheme 39). The reaction of alkenes **39.1** possessing an 8-quinolylamide group as the directing group and alkyl tosylates in the presence of an iron catalyst give the corresponding (*Z*)-alkylated products **39.2** in good yield with perfect selectivity (Scheme 39) [49].
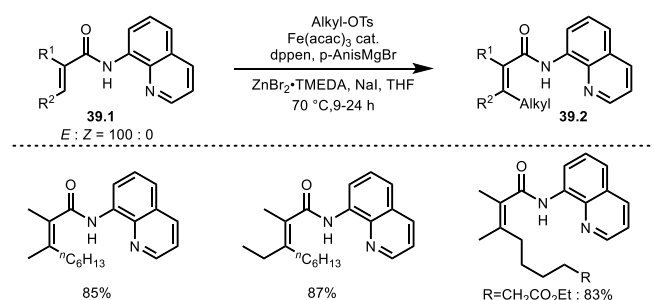


**Scheme 39.** Selective C-H alkylation

## Conclusion

In this review, we have summarized selected examples of the M-H reaction with less reactive internal olefins. The M-H reaction with a terminal olefin widely employed for the synthesis of *trans* internal olefins, but the corresponding reactions of internal olefins suffer from low reactivity and poor selectivity. Based on the reaction mechanism of the M-H reaction, *trans* internal olefins should give *E*-products and *cis* internal olefins should give *Z*-products. This can be explained by using a Newman projection of the corresponding carbometallated intermediate, which is generated from the reaction of R-M-X and an olefin. In the case of the arylative M-H reaction, most of the cases have employed trans olefins to give products with good to perfect (*E*)-selectivity. The corresponding alkylative reactions, however, have a tendency to result in low yields of the products poor selectivity. Moreover, convergent M-H reactions with *E* and *Z*-mixed olefins have not yet been established in either case. This remains one of the key outstanding challenges in this research area.

## Acknowledgements

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# REVIEW

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**The Mizoroki-Heck reaction with internal olefins: Reactivities and stereoselectivities**

Layout 2:

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